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PRINCIPAL INVESTIGATOR: Habibul Ahsan, M.D.

CONTRACTING ORGANIZATION: Columbia University in the  
City of New York  
New York, New York 10032

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<b>E-MAIL:</b> ha37@columbia.edu						
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<b>13. ABSTRACT (Maximum 200 Words)</b> Previous studies indicate that circulating estradiol is significantly elevated in breast cancer patients compared to controls in high and low risk populations. A variation in enzyme activity, i.e., the polymorphism of genes encoding the enzymes responsible for the metabolism and binding of estrogen may be related to an altered risk of breast cancer. The cytochrome P45017 $\alpha$ , an enzyme involved in estrogen biosynthesis has shown the most potential in the etiology of breast cancer. In this study we investigated whether a polymorphism of the CYP17 gene, involved in the biosynthesis of estrogen, is associated with an altered risk of breast cancer among a population-based sample of women (400 cases and 400 controls) participating in the Long Island Breast Cancer Study Project. We also explored whether the effects of reproductive risk factors and exposure to exogenous estrogen or estrogen-like substances are modified by the CYP17 polymorphism. In addition we are investigating the relation between urinary estrogen metabolites and the CYP17 polymorphism. Since this polymorphism is prevalent in the population, it may potentially contribute to a high population attributable risk. Unfortunately, at this time, due to the politically sensitive nature of the parent Long Island project (P.I. Marilie Gammon) we are not permitted to release the actual results of this.						
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#### **4) Introduction**

The long term goal of this research is to examine whether polymorphisms of genes involved in the biosynthesis and metabolism of estrogen, the key factor in breast cancer etiology, is related to an altered risk of breast cancer in women. The present study focuses on a polymorphism in the CYP17 gene which catalyzes the early steps of estrogen biosynthesis pathway. The variant allele of this polymorphism (A2) is associated with an increased expression of the gene (Feigelsen et al, 1998) and has been shown to be associated with an increased risk of breast cancer among its carriers (Feigelsen et a, 1997; Bergman-Jungestrom et al, 1999). Since CYP17 is involved in estrogen biosynthesis, it is possible that effects of reproductive risk factors (age at menarche, menopause and last child birth and parity) and exposure to exogenous estrogens or estrogen-like substances, e.g., hormone replacement therapy, oral contraceptives and organochlorine pesticides on breast cancer would be modified by the CYP17 genotype. Since we also have laboratory data on the urinary estrogen metabolites ( $16\alpha$  and  $12\alpha$ -hydroxyestrone) on the study participants as part of the parent project we are also examining whether these metabolites correlate with CYP17 genotype.

#### **5. Body**

- Task I: During months 1-2 of this grant we randomly selected 400 cases and 400 controls in batches using code numbers from the total 1200 cases and 1200 controls respectively from the parent study who completed the questionnaire and have provided samples. We also identified DNA samples for each of these 400 cases and 400 controls which were isolated and stored as part of the parent Long Island Breast Cancer Study Project (LIBCSP).
- Task II: During months 3-12, laboratory assays for CYP17 genotyping on these 400 cases and 400 controls were performed. The DNA was PCR amplified using CYP17

specific primers and digestion of the DNA was performed using specific restriction enzymes. Gel electrophoresis was used to detect RFLPs.

- | Task III: Laboratory data were entered into the computer and were merged with the main questionnaire data.
- | Task IV: Data analysis has been completed.
- | Task V: Manuscript preparation and report writing are being done.

**6. Key Research Accomplishments:** Not applicable at this time.

**7. Reportable Outcomes:** Not applicable at this time.

**8. Conclusions:** Not applicable at this time.

**9. References:**

Bergman-Jungestrom, et al. Association between CYP17 gene polymorphism and risk of breast cancer in young women. Int J Cancer, 1999; 84(4): 350-353.

Feigelsen, et al, Cytochrome P450c17alpha gene polymorphism is associated with serum estrogen and progesterone concentrations. Cancer Res. 1998; 58(4):585-587.

Feigelsen, et al. A polymorphism in the CYP17 gene increases the risk of breast cancer. Cancer Res, 1997;57(6): 1063-5.

**10. Appendices:** None